

# Long-Term Survival in Patients With Resting Obstructive Hypertrophic Cardiomyopathy

## Comparison of Conservative Versus Invasive Treatment

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<b>Objectives</b>	The aim of this study was to compare the survival of patients with hypertrophic cardiomyopathy (HCM) and resting left ventricular outflow tract (LVOT) obstruction managed with an invasive versus a conservative strategy.
<b>Background</b>	In patients with resting obstructive HCM, clinical benefit can be achieved after invasive septal reduction therapy. However, it remains controversial whether invasive treatment improves long-term survival.
<b>Methods</b>	We studied a consecutive cohort of 649 patients with resting obstructive HCM. Total and HCM-related mortality were compared in 246 patients who were conservatively managed with 403 patients who were invasively managed by surgical myectomy, septal ethanol ablation, or dual-chamber pacing.
<b>Results</b>	Multivariable analyses (with invasive therapy treated as a time-dependent covariate) showed that an invasive intervention was a significant determinant of overall mortality (hazard ratio: 0.6, 95% confidence interval: 0.4 to 0.97, $p = 0.04$ ). Overall survival rates were greater in the invasive (99.2% 1-year, 95.7% 5-year, and 87.8% 10-year survival) than in the conservative (97.3% 1-year, 91.1% 5-year, and 75.8% 10-year survival, $p = 0.008$ ) cohort. However, invasive therapy was not found to be a significant independent predictor of HCM-related mortality (hazard ratio: 0.7, 95% confidence interval: 0.4 to 1.3, $p = 0.3$ ). The HCM-related survival was 99.5% (1 year), 96.3% (5 years), and 90.2% (10 years) in the invasive cohort, and 97.8% (1 year), 94.6% (5 years), and 86.9% (10 years) in the conservative cohort ( $p = 0.3$ ).
<b>Conclusions</b>	Patients treated invasively have an overall survival advantage compared with conservatively treated patients, with the latter group more likely to die from noncardiac causes. The HCM-related mortality is similar, regardless of a conservative versus invasive strategy. (J Am Coll Cardiol 2011;58:2313–21) © 2011 by the American College of Cardiology Foundation

Hypertrophic cardiomyopathy (HCM) is a genetic disorder of the cardiac sarcomere (1–3). Asymmetric septal hypertrophy is the most common manifestation of this condition, and a significant number of patients have associated left ventricular outflow tract (LVOT) obstruction (4–6). The long-term prognosis of patients with HCM and LVOT obstruction in the contemporary era remains unclear. Patients with New York Heart Association (NYHA) functional class III/IV symptoms are generally started on pharmacotherapy (5). In patients

who remain symptomatic or who become intolerant of medications, an invasive intervention is warranted. Invasive therapeutic options include surgical myectomy, dual-chamber (DDD) permanent pacing, or septal ethanol ablation (SEA) (5). Although significant hemodynamic and clinical benefit can be achieved after invasive relief of the LVOT obstruction, it remains controversial whether abolition of the LVOT gradient actually improves long-term survival (7).

One large observational study has demonstrated that patients with HCM and LVOT obstruction have a worse long-term prognosis when compared with patients without obstruction (6). However, there are no randomized trials of medical versus invasive therapy, and the majority of retrospective cohort studies were done before the modern era. Another study suggested that patients with LVOT obstruction managed with surgical myectomy

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## Abbreviations and Acronyms

<b>CI</b>	= confidence interval
<b>DDD</b>	= dual-chamber
<b>HCM</b>	= hypertrophic cardiomyopathy
<b>LVOT</b>	= left ventricular outflow tract
<b>NYHA</b>	= New York Heart Association
<b>SCD</b>	= sudden cardiac death
<b>SEA</b>	= septal ethanol ablation
<b>TGH</b>	= Toronto General Hospital

## Methods

**Study population and data collection.** This study included consecutive adult patients ( $\geq 18$  years of age at initial presentation to the Toronto General Hospital [TGH]) with resting obstructive HCM who were referred to our institution between 1986 and 2007. Some of these patients were included in previous publications from our institution (9,10), but clinical and echocardiographic follow-up were updated from the time of completion of these studies. The diagnosis of HCM was established by the presence of asymmetric septal hypertrophy (septum  $\geq 13$  mm), in the absence of another condition that could account for the degree of hypertrophy observed (5). Echocardiographic data were obtained, as described previously (11), and LVOT gradients were determined by continuous wave Doppler assessment (11,12). Only patients with resting LVOT obstruction, defined as a resting gradient of  $\geq 30$  mm Hg, were included. The following conditions excluded patients from this study: other congenital syndromes (e.g., Noonan's), a fibrous subaortic membrane, significant aortic stenosis (defined as an aortic valve area  $< 1.2$  cm<sup>2</sup> or peak gradient  $\geq 30$  mm Hg across aortic valve), HCM with midventricular obstruction, HCM with pure provocable LVOT obstruction (i.e., LVOT gradient  $< 30$  mm Hg at rest but  $\geq 30$  mm Hg only after provocation), significant valvular lesions (other than mitral regurgitation due to systolic anterior motion), and significant epicardial coronary artery disease (coronary stenosis [ $> 70\%$ ] on coronary angiography, previous bypass surgery, or percutaneous coronary intervention). Finally, we excluded patients who had previously undergone invasive procedures to treat their LVOT obstruction at other institutions.

**Management of patients with obstructive HCM: conservative and invasive management.** Over the course of the study period, the approach to the management of patients with obstructive HCM adhered to the following principles. Symptomatic patients were typically initially treated with medications (beta blockers, disopyramide, and/or calcium

have better survival than conservatively treated patients (8). However, in this study, the medically and surgically managed patients were treated at different institutions, raising issues of referral bias. Therefore, we sought to compare the survival of patients with obstructive HCM who were treated conservatively with those treated invasively at a single tertiary care referral center. We also evaluated the factors predicting long-term survival in patients with resting obstructive HCM.

channel blockers). Patients were referred for invasive management in the presence of unacceptable symptoms despite maximally tolerated medical therapy. The choice of invasive procedure (myectomy, SEA, or DDD pacing) was determined by the managing physician, taking into account the clinical profile of the patient, presence of comorbid conditions, and his/her individual preferences.

**Classification of patients.** Patients were classified into 2 groups: 1) the conservative group, comprising those patients who received only medications (or no therapy) throughout the entire follow-up period; and 2) the invasive group, comprising patients who underwent (at any point during the follow-up period) any of the following procedures for management of their LVOT obstruction: 1) surgical myectomy; 2) SEA; or 3) DDD pacing. Patients in the conservative group were subclassified according to clinical status. Patients in the invasive group might have received medical therapy at the time of presentation but were subsequently referred for an invasive procedure. If patients underwent more than 1 procedure to treat their LVOT obstruction, they remain categorized according to the initial invasive treatment. Although DDD pacing has largely fallen out of favor as a treatment strategy in patients with HCM and LVOT obstruction (5), we included patients who underwent DDD pacing in the invasively managed cohort, because pacing was considered a reasonable therapeutic option for much of the 1990s.

**Invasive procedures.** Surgical myectomy was performed, as previously described, throughout the study period (10). Dual-chamber pacing has been offered at TGH since the 1990s (13). Septal ethanol ablation has been available at our institution since 1998 (9).

**Follow-up and definition of outcomes.** The status of patients was determined by cross-sectional follow-up, with the most recent evaluation available in the last 2 years. We classified deaths as HCM-related or noncardiovascular. Deaths were considered to be HCM-related in the presence of 1 of the following: 1) death within 30 days of an invasive procedure; 2) sudden cardiac (nontraumatic) death (SCD); 3) heart failure-related death; or 4) stroke-related death. For our survival analyses, resuscitated cardiac arrest and appropriate implantable cardioverter-defibrillator discharges were treated as HCM-related and sudden deaths. Patients who underwent cardiac transplantation were censored at the time of transplantation. In instances when the cause of death could not be determined, an HCM-related cause of death was ascribed.

**Ethics.** This study was approved by the Research Ethics Board of our institution.

**Statistical analysis.** Continuous and categorical data were analyzed with *t* tests, Wilcoxon rank-sum tests, chi-square tests, or McNemar's test, where appropriate.

**MULTIVARIABLE MODELS.** The primary survival analyses were performed with the Cox proportional hazards model (14). Univariate and multivariable models were developed to

assess the independent determinants of overall and HCM-related mortality. All patients had the same start point in these models, defined at the date of the first visit at our HCM Clinic. Importantly, to evaluate the impact of invasive intervention on mortality, we treated the invasive intervention as a time-dependent covariate in the models for overall and HCM-related mortality. Therefore, in the invasively treated patients, the period before invasive treatment was treated in the model as survival due to noninvasive therapy, whereas the period from the date of the invasive intervention to the date of last follow-up was treated as survival due to invasive therapy. In the conservative group, the entire period of observation was thus treated as survival due to noninvasive therapy.

**KAPLAN-MEIER METHOD.** Kaplan-Meier survival curves were constructed to graphically represent overall and HCM-related survival in the conservative and invasive groups (15). By necessity, the periods of observation used in this analysis were different for these 2 groups. In the conservative group, the period of observation began at the date of the initial visit at TGH. However, in the invasive group, the period of observation began from the date of the invasive intervention. This method of representing the different observation times has been previously employed in this patient population (8). Differences in survival were compared with the log-rank test, and a *p* value <0.05 was considered statistically significant. All statistical analyses were performed with SAS (versions 9.1 and 9.2, Cary, North Carolina). In addition, we used NCSS/PASS

software (Kaysville, Utah) to calculate the statistical power of comparing survival in the invasive treatment groups.

## Results

**Baseline characteristics.** From 1986 to 2007, 649 patients with HCM and resting LVOT obstruction were referred to the TGH HCM Clinic (Table 1). At the baseline clinical assessment, invasively managed patients were 10 years younger ( $47 \pm 15$  years vs.  $57 \pm 16$  years, *p* < 0.0001), more symptomatic (60% NYHA functional class III/IV vs. 33%, *p* < 0.0001), had a thicker septum ( $22 \pm 5$  mm vs.  $20 \pm 5$  mm, *p* < 0.0001), and had a slightly higher resting gradient ( $70 \pm 33$  mm Hg vs.  $63 \pm 31$  mm Hg, *p* = 0.002), compared with the conservatively managed patients. Patients in the conservative group had a higher burden of major comorbidities (diabetes, malignancy, renal or liver dysfunction, gastrointestinal tract disorder, previous stroke) than patients in the invasive group (18.3% vs. 8.4%, respectively, *p* = 0.0002) (Table 1).

**Rationale for conservative therapy.** The majority of patients (81%) in the conservative group were continued on medical therapy, because they reported mild (NYHA functional class I/II) symptoms during follow-up. The remainder of the patients were NYHA functional class III/IV but had not undergone an intervention for the following reasons: 1) 13 patients were still undergoing a trial of medications at the time of the last visit; 2) 10 patients were accepted for an invasive procedure but were still awaiting

**Table 1** Baseline Characteristics

Baseline Study Population	Conservative Group (n = 246)	Invasive Group (n = 403)	Total (n = 649)	p Value
Age, yrs	57 ± 16	47 ± 15	51 ± 16	<0.0001
Male	122 (50%)	243 (60%)	365 (56%)	0.0006
Clinical status				
Shortness of breath	181 (73.6%)	347 (86.1%)	528 (81.4%)	<0.0001
Chest pain	133 (54.1%)	289 (71.7%)	422 (65.0%)	<0.0001
Syncope	33 (13.4%)	106 (26.3%)	139 (21.4%)	<0.0001
NYHA functional class I or II	164 (66.7%)	161 (40.0%)	325 (50.1%)	<0.0001
NYHA functional class III or IV	82 (33.3%)	242 (60.0%)	324 (49.9%)	<0.0001
Drug therapy				
Beta-blockers	141 (57.3%)	241 (59.8%)	382 (58.9%)	NS
Disopyramide	60 (24.4%)	187 (46.4%)	247 (38.1%)	<0.0001
Calcium-channel blockers	26 (10.6%)	48 (11.9%)	74 (11.4%)	NS
Comorbidities				
Diabetes	20 (8.1%)	12 (3.0%)	32 (4.9%)	0.003
Renal/hepatic dysfunction	10 (4.1%)	5 (1.2%)	15 (2.3%)	0.03
GI tract disorder	12 (4.9%)	5 (1.2%)	17 (2.6%)	0.009
Malignancy	6 (2.4%)	10 (2.5%)	16 (2.5%)	NS
Prior stroke	4 (1.6%)	4 (1.0%)	8 (1.2%)	NS
Any above comorbidity	45 (18.3%)	34 (8.4%)	79 (12.2%)	0.0002
Echocardiography				
Septal thickness, mm	19.9 ± 4.6	21.8 ± 5.3	21.1 ± 5.2	<0.0001
Left atrial diameter, mm	44.4 ± 7.3	45.9 ± 7.5	45.4 ± 7.4	0.016
Resting LVOT gradient, mm Hg	63.1 ± 30.8	70.4 ± 33.0	67.6 ± 32.4	0.002

Values are mean ± SD or n (%).

GI = gastrointestinal; LVOT = left ventricular outflow tract; NYHA = New York Heart Association.

the intervention at the time of the last assessment; 3) 13 patients were advised but refused to undergo an invasive procedure; and 4) 10 patients were not offered an intervention because of serious comorbidities.

**Invasive procedures.** Over this 21-year period, 246 patients were managed conservatively, whereas 403 patients underwent an invasive procedure. There was 1 death in a patient while awaiting an invasive intervention (SEA)—this patient was classified in the conservative group, because he had not undergone intervention before his death. In the invasively managed group, the mean duration of conservative therapy before the invasive intervention was  $1.6 \pm 2.6$  years (range, 1 day to 15 years), totaling 652 patient-years of conservative management. At the time the decision was made to proceed with an intervention, the majority of patients had NYHA functional class III/IV symptoms. There were 107 patients with NYHA functional class I/II symptoms, for whom invasive treatment was felt to be justified: 1) 87 patients had unacceptable symptoms or intolerable side effects from medications; 2) 16 patients developed symptomatic atrial fibrillation; and 3) 4 patients had a previous cardiac arrest in the presence of significant LVOT obstruction. Surgical myectomy was performed in 287 patients, SEA was performed in 85 patients, and DDD pacemaker implantation was performed in 31 patients.

**Peri-procedural complications.** The overall rate of serious peri-procedural complications was very low for all invasive procedures. In the myectomy group, there was 1 death (0.3%), 4 ventricular septal defects (1.6%), 3 strokes (1.2%), and 18 patients (6.2%) requiring a permanent pacemaker in the early post-operative period. There were no peri-procedural deaths in the SEA group. However, unwanted

myocardial infarction (distant from the targeted septum) occurred in 2 patients (2.1%), and there was 1 coronary dissection (necessitating urgent bypass surgery and myectomy). A permanent pacemaker was required in 22 patients (25.9%) after SEA. In patients managed with DDD pacing, there were no serious peri-procedural complications.

**Long-term clinical follow-up.** The mean follow-up duration was  $7.2 \pm 5.5$  years. Forty-two patients (6.5%) were lost to follow-up. The majority of these patients (71%) lived outside our metropolitan area and follow-up could not be obtained. Twenty-four (57%) of the patients whose recent clinical status could not be ascertained had  $>3$  years of follow-up. Improvements in the clinical and hemodynamic status are summarized in Table 2. The 2 main reasons for continued pharmacotherapy in the patients in the invasive group were the following: 1) 101 patients were being managed for atrial/supraventricular arrhythmias; and 2) 95 patients had ongoing LVOT obstruction (resting LVOT gradient  $\geq 30$  mm Hg in 16 patients, provokable LVOT gradient  $\geq 30$  mm Hg in 79 patients). Patients in the invasive cohort who remained on medications were significantly more likely to have: 1) undergone DDD pacing or SEA instead of myectomy; 2) been older at the time of invasive intervention; and 3) had a higher provokable LVOT gradient during follow-up ( $28.5 \pm 25.3$  mm Hg vs.  $16.5 \pm 14.1$  mm Hg,  $p < 0.0001$ ), compared with patients who were not receiving cardiac medications at the time of their last follow-up. A minority of patients (2.7%) in the invasive group required a second intervention to treat persistent symptomatic LVOT obstruction after their index procedure: 7 of 31 (22.6%) of the DDD pacing patients required subsequent SEA ( $n = 3$ ) or myectomy ( $n = 4$ ), and

**Table 2** Clinical and Echocardiographic Data at Last Follow-Up Visit

	Conservative Group	p Value (Baseline vs. Last Follow-Up)	Invasive Group	p Value (Baseline vs. Last Follow-Up)
Clinical status				
NYHA functional class I/II				
Baseline	67%	<0.0001	40%	<0.0001
Last follow-up	86%*		87%*	
Medications				
Beta-blockers				
Baseline	57%	0.003	60%	0.01
Last follow-up	87%		51%	
Disopyramide				
Baseline	24%	0.001	46%	<0.0001
Last follow-up	62%		12%	
Calcium-channel blockers				
Baseline	11%	NS	12%	NS
Last follow-up	12%		12%	
Resting LVOT gradient, mm Hg				
Baseline	63 ± 31	<0.0001	70 ± 33	<0.0001
Last follow-up	44 ± 35†		11 ± 13†	

\*p = NS between conservative and invasive groups at the time of last follow-up. †p < 0.0001 between conservative and invasive groups at the time of last follow-up.

Abbreviations as in Table 1.



**Table 3 Overall Mortality and Equivalents of Mortality**

	Conservative Group (n = 246)	Invasive Group (n = 403)	Total (n = 649)
<b>Mortality</b>			
HCM-related mortality	19 (7.7)	28 (6.9)	47 (7.2)
Sudden cardiac death	8 (3.3)	7 (1.7)	15 (2.3)
Non-HCM-related death	16 (6.5)	8 (2.0)	24 (3.7)
Overall mortality	35 (14.2)	36 (8.9)	71 (10.9)
<b>Equivalents of mortality</b>			
Resuscitated cardiac arrest	2 (0.8)	4 (1.0)	6 (0.9)
Appropriate ICD discharge*	1 (0.4)	3 (0.7)	4 (0.6)
Total mortality and equivalents of mortality	38 (15.4)	43 (10.7)	81 (12.5)

Values are n (%). \*A total of 55 patients (8.5% of the study cohort) received an implantable cardioverter-defibrillator (ICD) (for primary prevention [on the basis of presence of risk factors for sudden death] or secondary prevention).

HCM = hypertrophic cardiomyopathy.

4 of 85 (4.7%) of the SEA patients required subsequent myectomy at  $1.7 \pm 0.9$  years after the SEA procedure. None of the patients in the myectomy group required a second intervention to treat ongoing obstruction.

**Overall and HCM-related survival.** There were a total of 81 (12.5%) deaths (including resuscitated cardiac arrests and appropriate implantable cardioverter-defibrillator discharges) in the entire study cohort (Table 3). Three patients, all in the invasive group, underwent cardiac transplantation (after myectomy) and were censored at the time of these events. Invasive therapy (treated as a time-dependent covariate) was a significant determinant of overall mortality (hazard ratio [HR]: 0.6, 95% confidence interval [CI]: 0.4 to 0.97,  $p = 0.04$ ). The other significant predictors of overall mortality on multivariable analysis were the following (Table 4): 1) age  $>50$  years (HR: 2.6, 95% CI: 1.6 to 4.3,  $p < 0.0001$ ); 2) female sex (HR: 2.0, 95% CI: 1.3 to 3.2,  $p = 0.002$ ); and 3) septal thickness  $\geq 20$  mm (median thickness) (HR: 1.7, 95% CI: 1.02 to 2.7,  $p = 0.04$ ). The presence of a resting LVOT gradient  $\geq 64$  mm Hg (median LVOT gradient) was of borderline statistical significance (HR: 1.6, 95% CI: 0.98 to 2.5,  $p = 0.06$ ). In terms of HCM-related mortality, invasive therapy (as a time-dependent covariate) was not found to be a significant independent predictor (HR: 0.7, 95% CI: 0.4 to 1.3,  $p = 0.3$ ). The HCM-related mortality was predicted by 4

independent variables: 1) age  $>50$  years (HR: 2.0, 95% CI: 1.1 to 3.4,  $p = 0.01$ ); 2) female sex (HR: 2.1, 95% CI: 1.2 to 3.6,  $p = 0.006$ ); 3) septal thickness  $\geq 20$  mm (HR: 2.0, 95% CI: 1.1 to 3.6,  $p = 0.02$ ); and 4) resting LVOT gradient  $\geq 64$  mm Hg (HR: 1.7, 95% CI: 1.0 to 3.0,  $p = 0.0496$ ). Kaplan-Meier estimates of overall and HCM-related survival are shown in Figures 1 and 2. Overall survival rates were greater in the invasive ( $99.2 \pm 0.5\%$  at 1 year,  $95.7 \pm 1.2\%$  at 5 years, and  $87.8 \pm 2.4\%$  at 10 years) than in the conservative cohort ( $97.3 \pm 1.1\%$  at 1 year,  $91.1 \pm 2.2\%$  at 5 years, and  $75.8 \pm 4.2\%$  at 10 years,  $p = 0.008$ ). However, there was no significant difference in HCM-related survival between the invasive ( $99.5 \pm 0.4\%$  at 1 year,  $96.3 \pm 1.2\%$  at 5 years, and  $90.2 \pm 2.3\%$  at 10 years) and the conservative ( $97.8 \pm 1.0\%$  at 1 year,  $94.6 \pm 1.7\%$  at 5 years, and  $86.9 \pm 3.3\%$  at 10 years,  $p = 0.33$ ) groups.

**CLASSIFICATION OF DEATHS.** A larger proportion of patients in the conservative group, which had a higher prevalence of coexistent medical conditions, died from noncardiac causes (6.5% vs. 2.0%,  $p = 0.003$ ) (Table 3). The majority of the noncardiac deaths were due to malignancy ( $n = 7$ ), severe intrinsic lung disease ( $n = 5$ ), or gastrointestinal/hepatic disorders ( $n = 3$ ). Patients who died from noncardiac causes were much older ( $71 \pm 13$  years vs.  $62 \pm 17$  years,  $p = 0.03$ ) at the time of death than patients who died of HCM-related causes.

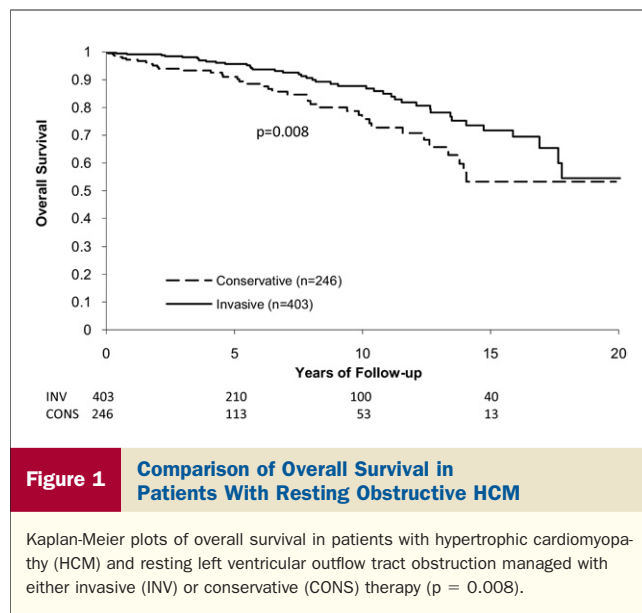
**INVASIVE TREATMENT GROUP: COMPARISON OF SURVIVAL AMONG THE DIFFERENT INVASIVE THERAPIES.** Within the cohort of invasively managed patients, there was a significant difference in total and HCM-related survival, depending on the invasive treatment selected. On multivariable analysis (with the time-varying covariate), there was no significant difference in overall survival between patients who underwent myectomy or SEA ( $p = 0.3$ ). Overall 1-year and 5-year survival were  $99.7 \pm 0.4\%$  and  $97.0 \pm 1.2\%$ , respectively, in the myectomy group and  $98.8 \pm 1.2\%$  and  $91.4 \pm 4.5\%$ , respectively, in the SEA group. The subset of patients who underwent DDD pacing had significantly worsened overall survival, with multivariable analysis (with the time-varying covariate) showing increased total mortality (HR: 2.6, 95% CI: 1.2 to 5.6,  $p = 0.02$ ). The corresponding 1- and 5-year overall survival in the DDD group

**Table 4 Clinical and Echocardiographic Predictors of Overall Mortality**

Variable*	Overall Survival HR (95% CI)	p Value	HCM-Related Survival HR (95% CI)	p Value
Age $>50$ yrs	2.6 (1.6–4.3)	$<0.0001$	2.0 (1.1–3.4)	0.01
Female	2.0 (1.3–3.2)	0.002	2.1 (1.2–3.6)	0.006
Septal thickness $\geq 20$ mm	1.7 (1.02–2.7)	0.04	2.0 (1.1–3.6)	0.02
Resting LVOT gradient $\geq 64$ mm Hg	1.6 (0.98–2.5)	0.06	1.7 (1.0–3.0)	0.0496
Invasive treatment†	0.6 (0.4–0.97)	0.04	—	0.30 (NS)

\*The group of patients without the indicated feature represents the reference category for the calculation of risk. †Variable treated as time-varying covariate.

CI = confidence interval; HR = hazard ratio.



was  $96.4 \pm 3.5\%$  and  $81.0 \pm 8.8\%$ , respectively. In terms of HCM-related survival, multivariable analysis (with the time-varying covariate) also revealed no significant difference in patients who underwent myectomy versus SEA ( $p = 0.6$ ). The HCM-related survival was worse in the pacing group (HR: 2.5, 95% CI: 1.01 to 6.03,  $p = 0.047$ ), compared with the other 2 interventions, myectomy and SEA, although this result was of borderline statistical significance. The HCM-related survival at 1 and 5 years was  $99.7 \pm 0.4\%$  and  $97.0 \pm 1.2\%$ , respectively, in the myectomy group;  $98.8 \pm 1.2\%$  and  $92.8 \pm 4.3\%$ , respectively, in the SEA group ( $p = 0.3$  for myectomy vs. SEA); and  $95.2 \pm 4.5\%$  and  $90.5 \pm 4.3\%$ , respectively, in the pacing group. However, the analysis comparing the SEA and myectomy groups was insufficiently powered ( $<80\%$  power) to detect a statistically significant difference.

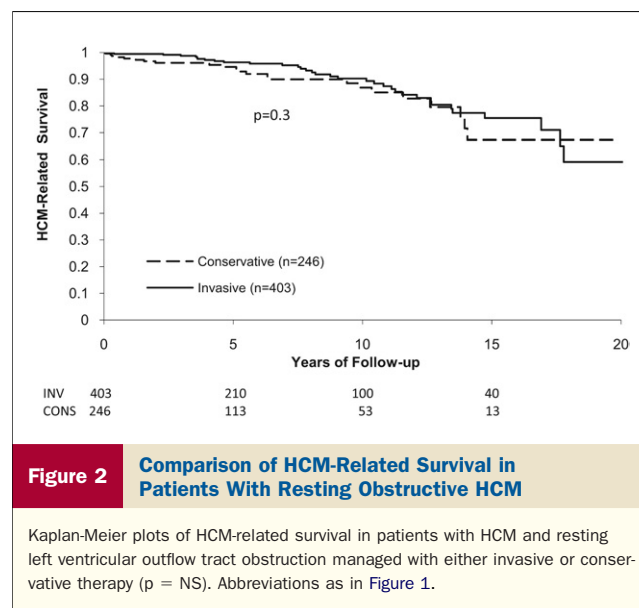
**COMPARISON OF SURVIVAL BETWEEN CONSERVATIVE THERAPY AND DIFFERENT TYPES OF INVASIVE TREATMENT.** We performed additional multivariable analyses of conservative versus invasive treatment, given the aforementioned worsened survival in the DDD pacing group, and specifically excluded the pacing cohort from the invasive group. These results showed that an invasive intervention was still associated with significantly improved overall survival (HR: 0.5, 95% CI: 0.3 to 0.8,  $p = 0.005$ ). The strength of this association with total survival was better when the pacing group was excluded rather than when it was included in the invasive cohort. However, there was still no difference in HCM-related survival between the conservative and invasive (myectomy and SEA patients only, excluding pacing group) cohorts on multivariable analysis ( $p = 0.13$ ). Furthermore, when we restricted our analysis to the conservative group versus the myectomy group (specifically excluding patients who underwent SEA or DDD pacing), there was a distinct survival advantage in the myectomy group in terms of

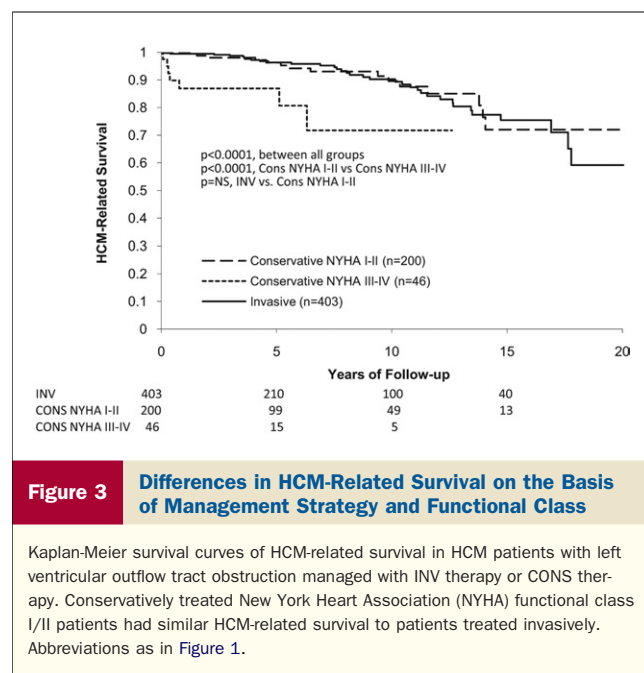
all-cause mortality (HR: 0.5, 95% CI: 0.3 to 0.8,  $p = 0.004$ ). Nonetheless, there was no significant difference in HCM-related survival between the conservative and the myectomy groups ( $p = 0.16$ ).

**Conservative management of obstructive HCM.** Multivariable analyses (with invasive intervention as a time-varying covariate) demonstrated that there was no significant difference in overall or HCM-related survival between the conservatively managed class I/II patients and the patients in the invasive group ( $p = 0.3$  and  $p = 0.7$ , respectively). Conservatively managed patients who were class I/II on medical therapy had significantly better HCM-related survival (100% at 1 year,  $96.3 \pm 1.7\%$  at 5 years, and  $89.6 \pm 3.4\%$  at 10 years) than those who were class III/IV at the time of the last assessment and who had not undergone an invasive intervention ( $86.9 \pm 5.5\%$  at 1 year,  $80.7 \pm 7.9\%$  at 5 years, and  $71.7 \pm 10.9\%$  at 10 years,  $p < 0.0001$ ) (Fig. 3).

## Discussion

**Summary of study findings.** In this large cohort of 649 patients with resting obstructive HCM, the majority of patients experienced an improvement in symptoms and in the degree of LVOT obstruction, either from increased medical therapy or from invasive therapy. Overall (but not HCM-related) survival was better in patients who underwent an invasive intervention. These outcomes between the conservative and invasive groups remained consistent in 2 additional circumstances: 1) when we excluded the DDD pacing group; and 2) when we considered the myectomy cohort alone in the invasive group (and excluded both the SEA and pacing groups). Patients in the conservative group were significantly older and sicker, with almost one-fifth of patients in the conservatively treated patients having a major comorbidity. A greater proportion of the conservative group





died from noncardiac causes. However, mildly symptomatic (NYHA functional class I/II) conservatively managed patients had survival similar to patients managed invasively.

**Conservative versus invasive therapy.** Much of the published data since the 1990s have demonstrated that myectomy is associated with excellent long-term survival (7,8,10,16,17). However, there have been few studies that have directly compared survival in invasively managed versus conservatively treated patients. It is well-established that septal myectomy (7,18), SEA (19), and, to a lesser extent, DDD pacing (20) improve symptoms. Whether abolition of the LVOT gradient and the resultant clinical and hemodynamic improvement translate to enhanced long-term survival remains controversial. Early studies comparing management strategies were confounded by high perioperative mortality that offset the apparent reduction in SCD provided by myectomy (21) and by inherent differences in the patient populations referred for surgical versus medical treatment (22).

A more contemporary comparison of invasively versus conservatively managed patients was conducted by Ommen et al. (8). This study compared 289 patients who underwent myectomy with 228 obstructive patients who were managed conservatively (and a third cohort of 820 patients with nonobstructive HCM was also described). Overall survival and freedom from HCM-related death were greater in the group treated with myectomy (83% [myectomy] vs. 61% [conservative] 10-year overall survival; 95% [myectomy] vs. 73% [conservative] 10-year freedom from HCM-related death). Although this study provides some evidence that myectomy might permit patients to achieve normal or near-normal longevity, there were some important differences between this study and our results. First, the invasively

and conservatively managed patients in the study by Ommen et al. (8) were treated at different institutions (all myectomy patients were treated at the Mayo Clinic [Rochester, Minnesota], whereas the nonoperated patients were managed at 1 of 3 other centers), introducing the possibility of significant referral bias. Second, our invasive cohort comprised patients who had any of the 3 types of septal reduction therapy, whereas the study by Ommen et al. (8) examined only the outcomes of myectomy patients versus conservatively managed patients. Third, there is a notable difference in the survival rates of the conservative groups in the 2 studies (61% 10-year overall survival in the study by Ommen et al. (8); 76% in our study), which suggests intrinsic differences between these 2 cohorts.

**Survival analyses comparing invasive versus noninvasive management.** Survival analyses involving patients undergoing an invasive procedure are inherently difficult because, by definition, all patients must have survived until the date of intervention. Within our cohort there was only 1 patient who died while awaiting an intervention, which minimized the effect of this potential survival bias in our study. In reality, patients are conservatively treated up until the date of their invasive procedure and thereafter cross-over to the invasive cohort. In our study, patients in the invasive group were managed conservatively for 652 patient-years before undergoing an invasive intervention. Invasive intervention was treated as a time-varying covariate in our multivariable models. Thus, these 652 patient-years were not discounted and, in fact, were treated in the multivariable models as survival due to noninvasive therapy.

**Clinical and echocardiographic predictors of long-term survival.** The independent determinants of HCM-related mortality (age >50 years, female sex, septal thickness  $\geq 20$  mm, and a resting LVOT gradient  $\geq 64$  mm Hg) identified in our study further contribute to our understanding of this condition. We and others have previously shown that increased age (10,23) and female sex (10,24) were associated with poorer outcomes in patients with HCM. The degree of hypertrophy might be regarded as a marker of severity and of increased risk of SCD in HCM (25). Studies in the past several years have consistently confirmed worsened survival in HCM patients with LVOT obstruction, compared with those without obstruction (6,26,27). However, whether the actual magnitude of the gradient is associated with increased mortality has been an unresolved issue. There was no association between the magnitude of the LVOT gradient and subsequent clinical deterioration in the study by Maron et al. (6). In contrast, 2 other large studies have shown a significant association between the degree of LVOT obstruction and overall survival (27,28). The latter study examined patients with minimally symptomatic obstructive HCM and also found reduced survival in patients at a threshold LVOT gradient of  $>64$  mm Hg (28).

**Clinical implications.** Our study represents the largest cohort of patients with resting obstructive HCM. The results of our study have several important clinical implica-



tions. First, the long-term survival of patients with conservatively treated obstructive HCM is much better than described in other studies (8,21,27). Second, our results suggest that symptom control and excellent HCM-related survival can be achieved with medical therapy. In our conservative cohort, the majority of patients received beta blockers (>80%) and/or disopyramide (>60%), which represent far higher rates of medication use than reported in other studies (6,8,27). Thus our study extends the findings of the multicenter study by Sherrid et al. (29), which provided evidence for meaningful symptom control in patients taking disopyramide. Third, our results demonstrate that medically treated class I/II patients with obstructive HCM have similar overall and HCM-related survival to patients treated invasively. The subset of conservatively treated patients who die prematurely are those very symptomatic patients who refuse invasive therapy or who have serious comorbidities that preclude an invasive intervention. Thus, despite the excellent reported outcomes for myectomy and SEA reported by experienced centers, our study lends support to current recommendations to only refer patients for invasive septal reduction therapy when they develop drug-refractory disabling symptoms (5). Fourth, in our large cohort of 403 invasively treated patients, we found no difference in 5-year survival between patients undergoing myectomy or SEA. The duration of follow-up for this cohort was longer than other previous studies comparing these 2 treatment strategies (30–34). This intermediate follow-up information contributes valuable data to the highly contentious debate surrounding the relative merits of myectomy versus SEA (35,36). Finally, our study results confirmed the findings of previous studies that have demonstrated poorer outcomes in patients who underwent DDD pacing (37).

**Study limitations.** We acknowledge certain limitations of the present study. This was a retrospective cohort study. It is unlikely that a prospective randomized controlled trial will ever be conducted in patients with obstructive HCM (38). As with any data from a tertiary care center, there might also be a referral bias. Clinically stable, asymptomatic, or older patients might be underrepresented in our cohort. In addition, given the clinical and technical expertise involved with both the conservative and invasive management of HCM, our results might not be generalizable to other centers. Even though this cohort is the largest dataset in the published reports of conservative versus invasive treatment in resting obstructive HCM, we are limited in the number of covariates that can be identified as significant in any 1 model, as with any study with a relatively small number of endpoints.

## Conclusions

Mortality attributable to HCM is similar, regardless of a conservative versus invasive strategy. However, patients treated with invasive therapy have an overall survival advantage compared with conservatively treated patients, with the

latter group more likely to die from noncardiac causes. There was no statistically significant difference in HCM-related survival between the conservative and invasive groups even when we reanalyzed the invasive cohort and 1) excluded the DDD pacing subset; and 2) only considered patients who underwent surgical myectomy. Increasing age, female sex, increased septal thickness, and a resting LVOT gradient  $\geq 64$  mm Hg are associated with worsened long-term survival.

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**Key Words:** ethanol ablation ■ hypertrophic cardiomyopathy ■ left ventricular outflow tract obstruction ■ myectomy ■ sudden cardiac death.